The mevalonate (MEV) pathway is an important metabolic pathway that produces steroid and isoprenoid precursors. *Methanocaldococcus jannaschii* (MjMK) is a key enzyme in regulating the MEV pathway. MK phosphorlates mevalonate using ATP to produce 5-phosphomevalonate (Figure 1).1,6

**Background**

**Research Questions:**
- What is the structural basis of the broad variation in MK inhibition profiles?
- How are inhibitors of different sizes able to bind to the same site?
- Why do some inhibitors weakly affect MK while others greatly affect MK, if at all?

**Previous Findings:**
- *MjMK* homologs that have crystal structures
- *Methanosarcina mazei* (MmMK) and *M. jannaschii* (MjMK) are inhibited by diphosphomevalonate (a different compound than the other inhibitors)
- Feedback resistant
- *Methanosarcina mazei* (MmMK)
- MK homologs whose inhibition has not been studied yet (inhibition not conclusive)
- *Methanocaldococcus jannaschii* (MjMK)
- *Leishmania major* (LmMK)

**Objectives & Methods**

**Objectives:**
- Obtain crystal structures of MjMK, SaMK, HsMK, ScMK bound to an inhibitor
- Perform parallel kinetic and inhibitions studies to complement the crystallographic work
- Use geranylgeranyl monophosphate (GGP), farnesyl monophosphate (FP), geranyl monophosphate (GPP), and isopentyl monophosphate to perform inhibition studies with the MK homologs
- Use geranylgeraniol, farnesol, geraniol, isopentenol to perform inhibition studies with the MK

**Methods:**
- Plasmid isolation & purification from *Escherichia coli*
- Transformation
- Bacterial cell culture & protein overexpression
- Cell lysis & protein purification
- Protein crystallization
- Kinetic & inhibition studies

**Conclusion**

- The mevalonate (MEV) pathway is an important metabolic pathway that produces isoprenoid precursors. Mevalonate kinase (MK) is a key enzyme in regulating the pathway.1,6
- Competitive feedback inhibition regulates MK with respect to ATP in many different organisms.
- MK homologs include crystallographic work.
- Crystal structures of MjMK, SaMK, HsMK, ScMK have been solved, including MK bound to ATP and inhibitor FSP.3
- The objectives of the study are to obtain structures of MjMK, SaMK, HsMK and ScMK bound to inhibitors, while characterizing them by performing kinetic and inhibition studies and determining if the phosphate groups are responsible for allowing the diverse group of MK inhibitors to bind to the same site.
- If this work is successful, it will provide insight into enzyme regulation and allow the creation of new antimicrobial drugs and isoprenoids used to treat various serious illnesses.1,6

**References**


**Acknowledgments**

I would like to thank my mentor Dr. Yan Kung and my lab members for educating me about the MEV pathway, MK, and HMG-CoA reductase (HMGCR), and for supplementing a research experience using online resources. Thanks also to Dr. Kung for helping me with this paper. I am also grateful to Bryn Mawr College for funding the Summer Research Science Program.